REMARKS

Amendments in the specification

The abstract is amended, as requested by the Examiner, to a single paragraph in narrative form having no more than 150 words.

Amendments in the claims

The following claims are pending in the present application following amendment herein: Claims 1–6, 8–13 and 15–18. Claim 7 was canceled by previous amendment.

Claim 14 is canceled herein without prejudice in order to expedite prosecution. Applicant reserves the right to pursue presently canceled subject matter in one or more continuing applications.

Claims 1, 11 and 12 are amended herein to further improve clarity, for example by improved antecedent basis.

No new matter is added, and no change in inventorship is believed to result from amendment of the claims as proposed herein.

RESPONSE TO OFFICE ACTION DATED FEBRUARY 2, 2009

1. Objection to the abstract

The abstract of the application is objected to as not being in accordance with MPEP §608.01(b). Applicant replaces the abstract by amendment herein and believes the present objection is thereby overcome. Withdrawal of the present objection to the abstract is respectfully requested.

2. Rejection of Claim 14 under 35 U.S.C. §112, first paragraph

Claim 14 stands rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph. Claim 14 is canceled herein, therefore the present rejection is now moot. Withdrawal of the rejection of Claim 14 under 35 U.S.C. §112, first paragraph, is respectfully requested.

3. Rejection of Claims 1–5, 8 and 10–18 under 35 U.S.C. §112, first paragraph

Claims 1–5, 8 and 10–18 stand rejected for allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph. Specifically, the Examiner alleges that the specification does not contain adequate written description to

support the recitation "amine-functional drug." In support of this rejection, the Examiner asserts (Action, p. 7):

> ... claim(s) 1–5, 8 and 10–18 [are] directed to encompass any amine functional drug, which only corresponds in some undefined way to specifically instantly disclosed chemicals. ... Applicants have provided no definition as to what constitutes an amine functional drug except indicating four specific drugs that are considered amine functional drugs.

This rejection is respectfully traversed.

To determine compliance with the written description requirement, "the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention now claimed. See MPEP 2163.02 citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), emphasis added. Applicant submits that the specification as a whole conveys with reasonable clarity to one skilled in the art that it was in possession of the genus "amine-functional drug" for at least the facts and reasons below:

1. Although not required, there is *in haec verba* support for the term "amine-functional drug" throughout the specification. See MPEP 2163.03.
2. "A further object and aspect of the present invention is to provide a suitable composition and manufacturing methods of polymer matrices in TDS which lead to an enhanced delivery of weakly basic amines to and across the skin ..." (specification as filed at p. 2, lines 24–27, emphasis added).
3. "Fig. 1 shows the effect of the protonation of the drug in the semi-permeable matrix on the drug absorption" (specification as filed at p. 3, lines 28–29, emphasis added).
4. "Fig. 3 shows the effect of reducing the amount of the protonated form of the drug in the semi-permeable matrix ..." (specification as filed at p. 3, lines 35–36, emphasis added).
5. "Surprisingly, it was found that drug release properties of a TDS having a silicone-type matrix containing an amine functional drug can be significantly enhanced by (1) minimizing the amount of the amine functional drug which is present in the protonated form (salt form) ..." (specification as filed at p. 4, lines 24–29, emphasis added).

6. "Particularly preferred amine functional drugs are dopamine D2 agonists ..."; "[e]specially preferred dopamine D2 receptor agonists are [aminotetralin] compounds ..." (specification as filed at p. 6, lines 1–7, emphasis added).
7. "Other examples of particularly preferred amine functional drugs are N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]propanamide (INN: fentanyl) which is useful in the treatment of pain and anticholinergic drugs ..." (specification as filed at p. 6, lines 9–12).
8. "Examples of such anticholinergic drugs which are useful in the present invention are 4-diethylamino-2-butynyl phenyl-cyclohexyl-glycolate (INN: [oxybutynin]) and 2-[3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl isobutyrate (INN: fesoterodine)" (specification as filed at p. 6, lines 14–19).
9. The distinction between the protonated (*i.e.*, salt) and free base form of the amine functional drug is supported throughout Applicant's specification. For instance, see all of the Examples, including "Comparative Examples", in the specification as filed.

Additionally, "factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure ... [and] description of a representative number of species reduced to practice ... or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties ... or by a combination of such identifying characteristics ..." MPEP 2163.II.A.3(a)(i) and (ii).

The Examiner asserts that "amine-functional drug" is a functional description (Action, p. 9–10), relying on *University of Rochester v. G.D. Searle*, 69 USPQ2d 1886 (Fed. Cir. 2004). Applicant respectfully submits that this assertion is mistaken. The genus "amine-functional drug" is not defined functionally as a "description of what a material does, rather than of what it is" (*Rochester* citing *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)). In stark contrast, "amine-functional drug" herein is a description of a shared structural feature of the drug, not what the drug "does." It is well known in the art that amines are "functional" groups that contain a basic nitrogen atom with a lone pair of electrons, and thus can accept hydrogen ions, *i.e.*, are protonatable. Thus, contrary to the Examiner's assertion, one of ordinary skill in the art can easily envision, and

indeed recognizes, that an "amine-functional drug" is a drug containing a protonatable amine group; and one can easily find such drugs, for example in The Merck Index.

Further, the claimed genus is not "highly variant" as asserted by the Examiner (Action, p. 9). Each drug species in the genus contains a protonatable amine group. Applicant's disclosure of four drugs containing such a group is representative of the genus "amine-functional drug" and is more than enough to solidify the skilled artisan's understanding of the metes and bounds of the claimed genus. Therefore, the specification as a whole clearly conveys to one skilled in the art, that Applicant was in possession of the genus "amine-functional drug" at the time of filing.

With regard to Claim 10, the Examiner states that "Applicants have only indicated particles that can absorb salts of the amine functional drug are silica" (Action, p. 7). Applicant notes the Examiner's acknowledgement that disclosure at p. 10, lines 24–34 of the specification as filed provides *in haec verba* support for Claim 10, and, therefore, that the specification conveys that Applicant was in possession of the invention recited in Claim 10, thereby meeting the written description requirement. See MPEP 2163.03.

Lastly, with regard to Claims 3 and 4, citing Quan, *infra*, at p. 15, the Examiner states that the pKa of oxybutynin falls outside the range recited in Claim 4, and thus this "compound [oxybutynin] would not meet the limitations of this claim" (Action, p. 7). Applicant submits that oxybutynin is not required to meet the limitations of Claims 3 or 4. The claim which recites oxybutynin (Claim 9) is ultimately dependent on Claim 1, not Claims 3 or 4. Additionally, Quan does not specify which method was used to determine the pKa of oxybutynin; depending on which method was employed, results may vary. Further, the Examiner asserts that "[t]he specification does not specifically point out any drug that would meet the limitation of instant claims 3 or 4" (Action, passage bridging pp. 7–8). However, the Examiner admits, at p. 16 of the Action, when discussing Nugroho, that rotigotine has an octanol/water distribution coefficient at pH 7.4 of 3.41, which satisfies Claim 3. Therefore, as Applicant was clearly in possession of the invention as recited in Claims 3 and 4, the specification contains proper written description.

Withdrawal of the rejection of Claims 1–5, 8 and 10–18 under 35 U.S.C. §112, first paragraph, is respectfully requested.

4. Rejection of Claims 1–6, 10, 11 and 14–18 under 35 U.S.C. §103(a)

Claims 1–6, 10, 11 and 14–18 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over D'Angelo & Schur (U.S. Patent No. 5,932,240, herein "D'Angelo") in view of Mueller & Peck (U.S. Patent No. 6,884,434, herein "Mueller") as evidenced by Nugroho *et al.* (2004) Pharmaceutical Research 21(5):844-850, herein "Nugroho". This rejection is respectfully traversed.

Under *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), a claimed invention is considered obvious if the differences between the invention of the claim and the prior art are such that the subject matter of the invention of the claim as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.

To reach a proper determination under 35 U.S.C. §103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention as a whole would have been obvious at that time to that person. Knowledge of Applicant's disclosure must be put aside in reaching this determination. MPEP 2142.

In discussing the combination of D'Angelo and Mueller, the present Action alleges that it would have been obvious to a person of skill in the art "to add rotigotine free base to the transdermal delivery system ... because D'Angelo suggest[s] that drugs used to treat Parkinson's disease may be included in the microreservoirs of the transdermal patch and Mueller *et al.* is directed to transdermal delivery systems comprising rotigotine which is a drug taught as treating Parkinson's disease" (Action, p. 15, lines 3–8). However, the Action fails to acknowledge that the class of amine-functional drugs is not specified by D'Angelo. Parkinsonism control agents are mentioned in D'Angelo as only one class of drugs, embedded within a large list of other possible pharmacological actives. Additionally, rotigotine is not mentioned in D'Angelo's list of exemplary parkinsonism control agents (*i.e.*, bromotriptine, percolide, and anticholinergics including benzotropine, pro-cyclidine and amantadine). Nothing in D'Angelo would motivate one of ordinary skill to select the class of amine-functional drugs among the large list of allegedly possible pharmacological agents. In fact,

the exemplary list of drugs is prefaced with the statement that "almost any drug, to some degree, can be administered transdermally" (D'Angelo, col. 1, lines 58–59). Therefore, Applicant submits that the combination of D'Angelo and Mueller can only be made, impermissibly, by hindsight reconstruction of the invention based on the disclosure of the present specification. Applicant submits that, at least for this reason, a *prima facie* case of obviousness has not been established.

All claim limitations must be considered in judging the patentability of a claim against the prior art. MPEP 2143.03. Even if a sound rationale for combining the references has been articulated (which is not admitted herein), the resulting combination fails to teach or suggest all claim limitations. If the references are missing claimed features, there must be some apparent reason either in the references or the general knowledge in the art to modify the references to include the missing subject matter. *KSR*, *supra*.

According to Claim 1, the transdermal delivery system comprises a multitude of microreservoirs within a self-adhesive matrix, wherein the microreservoirs have a maximum diameter that is less than the thickness of the self-adhesive matrix. As described in more detail below, the combination of references fails to teach or suggest, at least, (a) microreservoirs within a self-adhesive matrix and/or (b) microreservoirs having a maximum diameter that is less than the thickness of the layer wherein they are embedded. For at least these reasons, a *prima facie* case of obviousness has not been established.

4.1. No teaching or suggestion of microreservoirs within a self-adhesive matrix

The present Action (p. 12) cites D'Angelo as allegedly disclosing an acrylate-based self-adhesive layer. However, without admitting that the "microcapsules" of D'Angelo necessarily equate to "microreservoirs" as recited in the instant claims, Applicant respectfully points out that the acrylate adhesive recited by D'Angelo is not the matrix within which microcapsules are incorporated, but a separate adhesive border used to adhere the patch to the skin. The "self-adhesive layer" referenced in the Action at p. 12, line 20 is misleading; the acrylate adhesive in D'Angelo is not a layer that either contains the microcapsules or lies over or under the microcapsule-containing layer. Rather it occurs in a border around the patch (D'Angelo, col. 8, lines 52–55).

The present Action states: "One would have been motivated to add rotigotine free base

[of Mueller] to the transdermal delivery system [of D'Angelo] ..." (p. 15). However, even if one of skill in the art would have been motivated to make such a modification (which is not admitted herein), that modification would not have provided microreservoirs within a self-adhesive matrix, as required by Claim 1.

The fact that D'Angelo mentions an acrylate adhesive and microcapsules as independent components of a patch is not sufficient to establish a *prima facie* case of obviousness. Under *KSR*, *supra* (emphasis added), "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. ... [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." The present Action's identification of a reference with microcapsules and a self-adhesive acrylate, each discussed independently in the reference, is exactly the type of hindsight reconstruction warned against in *KSR*. The combination of documents cited in the present Action does not provide an apparent reason for a person of ordinary skill to select and modify elements from the collective teachings to arrive at the present invention. *Id.* (an obviousness inquiry includes determining whether there was an apparent reason to combine the known elements in the fashion claimed).

No reason has been articulated to embed microreservoirs within the self-adhesive border as opposed to a gel matrix layer as disclosed by D'Angelo.

4.2. No teaching or suggestion of microreservoirs having a maximum diameter less than the thickness of the layer wherein they are embedded

D'Angelo fails to teach a transdermal system wherein the microreservoirs have a maximum diameter that is less than that of the self-adhesive layer. In stating that "it would have been obvious to one of ordinary skill in the art to vary ... the size of the microcapsule," the Examiner fails to recognize that Claim 1 requires more than simple manipulation of microreservoir diameter or thickness of a self-adhesive matrix layer. Specifically, Claim 1 requires a microreservoir diameter less than a maximum value relative to the thickness of the self-adhesive matrix layer.

Nothing in D'Angelo suggests that it would be beneficial for the microcapsules to have a maximum diameter less than the thickness of the matrix layer (in D'Angelo a gel matrix layer, not a self-adhesive matrix layer) in which they are embedded. Where relativity of microcapsule diameter and gel matrix layer is disclosed at all, it is clear that the microcapsules are contemplated by D'Angelo to be exposed to the surfaces of the matrix layer, *i.e.*, to have a diameter that is not smaller than the thickness of the matrix layer. Specifically, in D'Angelo's description of Figs. 1 and 2 thereof, a layer of microencapsulated medicament is said to be "adhered to the bottom of a tear strip **5** and to the top of a permeable membrane **13** by microcapsule adhesive **19**" (col. 8, lines 3–6). That the microcapsules themselves adhere to layers above and below the matrix layer is clear from Fig. 2. D'Angelo further emphasizes a means for disrupting the microcapsules, which in some embodiments is achieved by pulling back the tear strip, to which the "frangible" microcapsules are adhered (col. 8, lines 34–39). One of ordinary skill would be demotivated, by the teaching of D'Angelo regarding the significance of the disruption mechanism, to reduce the diameter of the microcapsules, such that the microcapsules no longer contact the layers above and below the matrix in which they are embedded.

Therefore, D'Angelo not only fails to disclose, but indeed teaches away from, a matrix layer containing microreservoirs of diameter smaller than the thickness of the matrix layer. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. MPEP 2145.X.*D*.3, citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Further, a modification of D'Angelo to reduce the size of the microcapsules would render the patch of D'Angelo unsatisfactory for its intended purpose. "If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." MPEP 2143.01.V, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). If microcapsule diameter were reduced so that the microcapsules no longer adhered to the tear-off strip, the patch of D'Angelo would no longer function as intended.

Alternatively, a modification of D'Angelo to reduce the size of the microcapsules would change the principle of operation of the D'Angelo patch. "If the proposed modification ... would change the principle of operation of the prior art invention being modified, then the

teachings of the references are not sufficient to render the claims *prima facie* obvious." MPEP 2143.01.VI, citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). If microcapsule diameter were reduced so that the microcapsules no longer adhered to the tear-off strip, the principle of operation of D'Angelo would be changed, indeed lost.

4.3. Mueller fails to supply the missing features

The secondary reference, Mueller, does not supply either one of the essential features of the present invention that are missing from D'Angelo, namely (a) microreservoirs within a self-adhesive matrix or (b) microreservoirs having a maximum diameter that is less than the thickness of the layer wherein they are embedded. Mueller, indeed, has no teaching or suggestion of microreservoirs at all. Thus no combination of the cited documents teaches or suggests all the claim limitations.

4.4. Rejection under 35 U.S.C. §103(a): conclusion

For any one of the reasons set forth above, a *prima facie* case of obviousness has not been established for instant Claim 1.

Notwithstanding the Examiner's remarks with respect to the subject matter of dependent Claims 2–6, 10, 11 and 14–18, these claims each embody all the limitations of Claim 1 from which they depend or which they reference, and are therefore nonobvious at least for the same reasons that Claim 1 is nonobvious. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. MPEP 2143.03.

However, Applicant respectfully takes issue with the Examiner's statements regarding polyvinylpyrrolidone (PVP), as these statements appear again to utilize the hindsight reconstruction warned against in *KSR*, *supra*. Specifically, the present Action alleges "that D'Angelo *et al.* teach PVP and Mueller *et al.* [teach] that if polyvinylpyrrolidone is added to the adhesive, the dissolving capacity for the free base in such matrices is increased" (p. 15, lines 18-20). Applicant submits that the discussion of PVP in D'Angelo is focused on use of PVP as a matrix and not as a component of the microcapsules; and Mueller does not teach microcapsules. Therefore, any combination of D'Angelo and Mueller (even if motivation existed for such combination, which, as shown above, is not the case) would not result in microcapsules containing PVP, but as a matrix in which the microcapsules are incorporated.

Furthermore, the Action states that "One of ordinary skill in the art would have been motivated to replace acrylate adhesives [of D'Angelo] with silicone adhesives as both are taught by Mueller *et al.* as functional equivalents." (p. 14, lines 18-22) Even if this were true, which is not admitted, addition of self-adhesive silicone to the adhesive component of the D'Angelo patch would not result in microcapsules within a self-adhesive matrix, but simply in additional self-adhesive for the patch border to adhere the patch to the skin.

Regarding Claims 3 and 4, the Examiner cites Nugroho only for reporting that the octanol/water distribution coefficient of rotigotine at pH 7.4 is 3.41. Applicant submits that neither this fact, nor anything else within Nugroho, provides support for (a) microreservoirs within a self-adhesive matrix or (b) microreservoirs having a maximum diameter that is less than the thickness of the layer wherein they are embedded. Nugroho relates to active drug delivery by iontophoresis, as opposed to passive transport as provided by the present TDS.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested for at least the reasons given above.

5. Rejection of Claims 8 and 9 under 35 U.S.C. §103(a)

Claims 8 and 9 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over D'Angelo in view of Mueller and Quan *et al.* (U.S. Patent No. 5,834,010, herein "Quan"). This rejection is respectfully traversed.

Claims 8 and 9 each embody all limitations of Claim 1, from which they ultimately depend. Applicant submits that Claims 8 and 9 are nonobvious over D'Angelo and Mueller for at least the same reasons as Claim 1 discussed in Section 4 above. Additionally, Quan is relied upon for allegedly reporting transdermal delivery of oxybutynin (Action, p. 17). However, Quan does not cure any of the deficiencies of D'Angelo or Mueller, and provides no motivation to modify the references to achieve either one of the essential features of the present invention that are missing from the cited references, namely (a) microreservoirs within a self-adhesive matrix or (b) microreservoirs having a maximum diameter that is less than the thickness of the layer wherein they are embedded. Thus no combination of the cited documents teaches or suggests all the claim limitations.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested for at least the reasons given above.

6. Rejection of Claims 12 and 13 under 35 U.S.C. §103(a)

Claims 12 and 13 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over D'Angelo in view of Mueller and Pfister & Wilson (U.S. Patent No. 5,232,702, herein "Pfister"), as evidenced by Nugroho. This rejection is respectfully traversed.

Claims 12 and 13 each embody all limitations of Claim 1, from which they ultimately depend. Applicant submits that Claims 12 and 13 are nonobvious over D'Angelo and Mueller as evidenced by Nugroho for at least the same reasons as Claim 1 discussed in Section 4 above. Additionally, Pfister is relied upon for allegedly reporting use of a low silanol-containing and high silanol-containing silicone adhesive. However, Pfister does not cure any of the deficiencies of D'Angelo or Mueller, and provides no motivation to modify the references to achieve either one of the essential features of the present invention that are missing from the cited references, namely (a) microreservoirs within a self-adhesive matrix or (b) microreservoirs having a maximum diameter that is less than the thickness of the layer wherein they are embedded. Thus no combination of the cited documents teaches or suggests all the claim limitations.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested for at least the reasons given above.

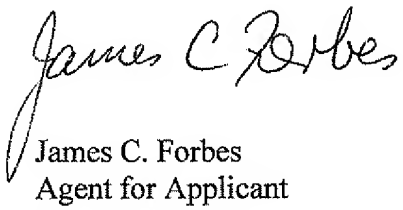
7. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



James C. Forbes
Agent for Applicant
Reg. No. 39,457
Tel. 847-412-6350